CONGENITAL ICHTHYOSIS IN PEDIATRIC AGE GROUP - A CLINICAL STUDY

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CERTIFICATE

Certified that this dissertation entitled "Congenital ichthyosis in pediatric age group – a clinical study" is a bonafide work done by **Dr.P.Sivayadevi** postgraduate student of the department of Dermatology, Venereology and Leprosy, Madras Medical College, Chennai- 600003, during the academic year 2005-2008. This work has not previously formed the basis for the award of any degree.

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CONTENTS

INTRODUCTION

Ichthyoses comprise of a heterogeneous group of disorders, due to defect in keratinization or cornification with abnormal differentiation and desquamation of epidermis. It is clinically characterized by dry rough skin with scaling over much or the entire body surface.

The terminology and nosology of congenital ichthyosis has continuously evolved and has lead to a confusing medley of different terms and classification systems. Recent advances in the molecular genetics has provided tools to categorize ichthyosis, on the basis of their underlying genetic defects.

A number of well defined types of ichthyoses have characteristic features and can be reliably diagnosed. But a specific diagnosis can be challenging in certain patients and families due to great clinical heterogeneity.

In general, determination of whether an ichthyosis is inherited or acquired, presented at birth or later in life, and whether it is limited to the skin or part of multisystem disorder, helps in diagnosis. Quality and distribution of scale, presence or absence of erythroderma, blistering,

associated abnormalities of skin adnexae are other useful clinical features. A thorough family history is essential for recognizing the inheritance pattern. Establishing the correct clinical diagnosis in a patient with ichthyosis is a prerequisite for making prognostic predictions, therapeutic decisions and offering genetic counselling.

REVIEW OF LITERATURE

CONGENITAL ICHTHYOSIS

SYNONYMS

Fish skin disease, Alligator skin disease, Sauriasis, Congenital hyperkeratosis.

HISTORY

- The term ichthyosis derives from the Greek root 'ichthys' for fish.
- First historic reference to ichthyosis appears in an Indian text in 250Bc – 'Ekakushtha, skin disease like scales of a fish'[1].
- Hystrix type ichthyosis – 'porcupine men' in the lambert family of Suffolk was reported by Machin (1732)
- Harlequin fetus – one of the first genodermatoses recorded by Oliver Hart (1750)[1].
- 'Ichthyosis nacree' described by Alibert (1806) is the most likely first well documented report of ichthyosis vulgaris.
- Willan (1808) – classified ichthyosis as a 'squamous disease'.

- Brocq (1902) - distinguished bullous and nonbullous[2] ichthyosiform erythroderma.
- Cockayne (1933) – first to use genetic classification of ichthyosis.
- Refsum's disease – described by Norwegian neurologist Refsum (1946)[4].
- Sjögren – Larsson syndrome- described by Swedish psychiatrists (1957).
- Wells and kerr (1965) - recognized X- linked ichthyosis[3].

CLASSIFICATION

Early classification was based on scale description

– ichthyosis larvata/ tarda/ mitis/ inversa.

Wells and Kerr classified ichthyosis according to inheritance pattern

- AD/ AR/ XLR.

Vanscott, Frost, Weinstern[5] –classified based on rates of epidermal turn over.

Retention ichthyoses

Ichthyosis vulgaris

Recessive X-linked ichthyosis

Lamellar ichthyosis

Hyperproliferative ichthyoses

Non-bullous ichthyosiform erythroderma

Bullous ichthyosiform erythroderma

Refsum's disease

Sjögren-Larsson syndrome

CONGENITAL ICHTHYOSES

MAJOR FORMS:

Ichthyosis vulgaris

X-linked recessive ichthyosis

Non- bullous ichthyosiform erythroderma

Lamellar ichthyosis

Harlequin ichthyosis

Bullous ichthyosiform erythroderma

Ichthyosis bullosa of Siemens

Ichthyosis hystrix

ICHTHYOSIFORM SYNDROMES:

Netherton's syndrome

Sjögren- Larsson syndrome

Neutral lipid storage disease

Refsum's disease

Kallman's syndrome

Multiple sulphatase deficiency syndrome

X-linked dominant ichthyosis

IBIDS (trichothiodystrophy)

KID syndrome

CHILD syndrome

Ichthyosis follicularis with alopecia and photophobia

Rud's syndrome

Congenital ichthyosis variants

Isolated genetic syndromes with ichthyosis

PATHOGENESIS:

The primary function of the stratum corneum is to provide a barrier to water loss, without which terrestrial life is not possible. Defective barrier function leads to increased transepidermal water loss, a characteristic feature of ichthyosis.

The stratum corneum is a double compartment system analogous to a brick wall, in which the corneocytes ("bricks") provide the structural building blocks, around which a lipid enriched extracellular matrix (the "mortar") is deposited, to provide the permeability barrier to systemic water loss[6]. These lipids,predominantly,the neutral lipids,cholesterol sulphate, free fatty acids,and the polar lipids,ceramides,form repeating units of electron-lucent and electron-dense membranes,termed lamellar unit structures, when visualized with ruthenium tetroxide.Two or three lamellar unit structures fill the intercellular domains of stratum corneum. Lipids are

delivered to this site through secretion of lamellar bodies at the stratum granulosum-stratum corneum interface. Lamellar bodies contain glycosylceramides, phospholipids and cholesterol sulphate, as well as certain hydrolytic enzymes[9]. Upon secretion, some of these enzymes process glycosylceramides and phospholipids to ceramides and free fatty acids respectively. Conversion of cholesterol sulphate to cholesterol by cholesterol sulphatase present on the cell membrane surface, leads to breakdown of the intercellular lipid lamellae, and resultant desquamation.

In addition to lipids,the mortar of inner stratum corneum contains corneodesmosomes that span adjacent corneocytes[7]. Proteolysis of corneodesmosomes is required for normal desquamation[8]. In normal skin, desmosome density and cohesion lessens in transit from lower to upper stratum corneum.

Disordered keratinization also results from alterations in structural proteins like cornified cell envelope and enclosed aggregated keratin filaments,which are the major components of the stratum corneum. Envelope precursors such as involucrin, loricrin, small proline- rich proteins and envoplakin, are synthesized late in stratification and then cross- linked by the action of transglutaminase enzymes, which are synthesized in the granular layer.The corneocyte

protein envelope is linked covanently to an outer ceramide layer, the lipid envelope, which also contains a variety of membrane associated glycoproteins such as the integrins. Keratin intermediate filaments are the major stress bearing cytoskeletal proteins. They are aggregated by interaction with filaggrin (filament aggregating protein), a basic histidine rich protein, stored as profilaggrin in keratohyaline granules.

Normal desquamation is an invisible process by which a single corneocyte or small clump of corneocytes detaches from its neighbours and shed. In the retention hyperkeratoses, normal epidermal homeostasis is maintained, but desquamation is retarded and corneocytes are shed in large clumps. In the hyperproliferative ichthyoses, epidermal homeostasis is disturbed, the process of desquamation is abnormal as well. Chronic barrier damage induces keratinocyte DNA synthesis and results in epidermal hyperplasia[10], with knock-on effects on the activity of cytokines, growth factors, calcium gradients, adhesion molecules and lytic enzymes.

ICHTHYOSIS VULGARIS

Synonyms

Ichthyosis simplex

Autosomal dominant ichthyosis

Most common of the inherited ichthyoses, with a reported incidence of 1 in 250[12]. It is an autosomal dominant disorder with variable phenotypic expression and penetrance, so severity can vary between generations and affected siblings.

Pathogenesis

Absence or decrease of filaggrin and its precursor, profilaggrin is seen in the epidermis from patients with ichthyosis vulgaris in biomedical studies[13] . Expression of mRNA is reduced[14].There may be selectively impaired post transcriptional control of profilaggrin synthesis or the profilaggrin gene may be influenced by other mutated genes[15]. Scale formation is thought to result from loss of water retaining aminoacids derived from filaggrin catabolism[16]. The hyperkeratosis is regarded as a retention keratosis resulting from increased adhesiveness of stratum corneum. Labelling with tritiated thymidine shows a normal rate of epidermal proliferation[18].

Pathology

In the epidermis, there is moderate degree of hyperkeratosis with a thin or absent granular layer. Hyperkeratosis often extends in to the hair follicles, resulting in large keratotic follicular plugs.

Clinical features

Scaling is obvious from two months of age or may be further delayed. Clinical symptoms and severity depend on season and climate, improving during the summer with increasing humidity, and worsening

in a dry, cold environment. It usually improves with advancing age[12] . Pruritus is not a problem but will be present if associated with atopy. Rarely hypohidrosis with heat intolerance may be present. Scaling is most pronounced on the extensor surfaces of the arms and lower legs. The groin and flexural areas are spared because of increased humidity in those regions.Coexistant atopic dermatitis may obscure this feature. Face is usually spared, if involved localizes to forehead and cheeks, perioral region. Scaling on the trunk is less pronounced and diaper area is spared.

Scales are white or grey, small, flaky or branny and semi adherent with turned up edges giving a "pasted- on" appearance. Palms and soles show accentuated skin markings – hyperlinearity, due to mild hyperkeratosis. If severe, furrows or painful fissures may occur on the heels.

Associations[17]

Keratosis pilaris- involves posterior arms, thighs and buttocks.

Atopic triad of asthma, hayfever and atopic dermatitis in as many as 25 – 50% patients.

Ocular manifestations and testicular cancer have been reported.

X LINKED RECESSIVE ICHTHYOSIS

An X linked recessive disorder, which almost exclusively affects the male patients.

Estimated incidence ranges between 1 in 2000 to 1 in 9500 male births[19].

Pathogenesis

It is due to the inheritance of mutated steroid sulfatase gene (90% deletion) on chromosome XP 22.32 from the carrier mothers[20]. Steroid sulfatase is a membrane bound microsomal enzyme responsible for hydrolyzing sulphate groups from cholesterol sulphate and sulfated steroid hormones. Continued hydrolysis of cholesterol sulphate during corneocyte transit from inner to outer stratum corneum is a critical step normally leading to desquamation. Due to decrease in enzyme activity, cholesterol sulphate accumulates in the scale, constituting 30% of stratum corneum lipids[21](normal 3%) .Concomitant placental steroid sulfatase deficiency causes inadequate deconjugation of DHEAS necessary for estrogen synthesis which in turn leads to failure to initiate labour[22].Altered sex hormone profile may in part explain the abnormal testicular development in some patients.

Pathology

Epidermis shows slightly thickened with orthokeratotic hyperkeratosis[23].

Granular layer is normal or slightly thickened.

Kinetic studies show normal rates of cell turn over.

Clinical features

Age of onset –In 75% patients, scaling is evident within first week of life[22] as pronounced peeling or desquamation.In 6% manifestations occur after 1 year[24].Scaling tends to increase throughout childhood spreading up from lower legs to the trunk. and stabilizes in the teens.Scaling diminishes in summer months. But does not subside with age.

Site

Scaling is more prominent on the extensor surface extremities with significant flexural surface involvement. Posterior and lateral part of neck is almost invariably involved- 'dirty neck disease'. Upper and lateral abdominal wall and preauricular facial skin are commonly affected. Palm /soles are spared.

Scales

Medium to large, polygonal, dull, light to dark brown scales with tight adherence to skin. Light grey scaling may be seen in face, scalp, axillae, flexor aspect of limbs.

Systemic manifestations

Comma shaped asymptomatic corneal opacities in slit lamp examination is seen in 50 to 90% of adult patients and 25% of carrier

females,due to stromal deposits in posterior surface of Descemet's membrane[25].

Cryptorchidism is seen in 25% patients[26].

Abnormalities of sperm count or motility and testicular cancer[27] independent of

cryptorchidism.

Inguinal hernia

Unilateral renal agenesis

Rare – epilepsy, acute lymphoblastic leukaemia, paraplegia / parapareis due to prolonged labour.

Diagnosis

Elevated serum cholesterol sulfate – 2000 to 9000 μg/dl

(Normal 80 - 200 μg/dl).

Abnormal mobility of low density ß lipoproteins (fast band 2mm beyond control) on standard agarose gel lipoprotein electrophoresis. Assay of steroid sulfatase activity in cultured amniocytes, fibroblasts, leukocyts, or scales[29].

Prenatal diagnosis – southernblot, or PCR analysis of chorionic villi or amniotic fluid.

Decreased estrogen levels in maternal urine.

COLLODION BABY

It is a descriptive term for the baby who is born encased in a transulcent, parchment like membranous covering resembling a dried film of collodion.

It is the usual presentation of congenital recessive ichthyoses[30] like non-bullous ichthyosiform erythroderma and lamellar ichthyosis[34.] Others include trichothiodystrophy, Sjögren Larsson syndrome, and Conradi Hünermann disease.

Clinical features

Babies are born prematurely. At birth, the neonate is covered with a taught, shiny and transparent membrane formed by the thickened stratum corneum that resembles a plastic wrap or clingfilm . It's tautness leads to ectropion, eclabion, hypoplasia of nasal and aural cartilage. Normal skin markings are obliterated.

The membrane dessicates and cracks around flexures during the first days of life and completely shed within first few weeks of life and often reveals an erythrodermic ichthyosis.

Variants – self healing type – lamellar exfoliation of newborn or (10-20%) spontaneously healing collodion baby[31].

localized type

Complications

Impaired thermal regulation and hypothermia

Increased transcutaneous water loss and hypernatremic dehydration leading to renal failure and neurologic equelae.

Sepsis as fissures provide a portal of entry for microorganisms.

Pneumonitis due to aspiration of squamous material shed in to the amniotic fluid.

Hypoxia due to inelasticity of collodion membrane leading to restricted lung movement.

Vascular obstruction and distal oedema due to constricting band.

Malnutrition due to impaired sucking.

Pathology

Compact hyperkeratosis with a thick eosinophilic PAS positive stratum corneum.

Biopsy should be deferred until transition into the underlying disease phenotype occur.

HARLEQUIN ICHTHYOSIS

Synonym:

Ichthyosis congenita gravior

The term is derived from the variegated textile pattern used to clothe medieval jesters. Very rare disease, inherited in a autosomal

recessive manner[35] but sporadic cases were reported due to new dominant mutation[36].

Pathogenesis

Massive accumulation of scales are caused by a reduced activity of keratinocyte serine / theronine protein phosphatase, which leads to a block in profilaggrin processing to filaggrin[37].

Expressions of calpain 1 which plays a important role in epidermal differentiation as a regulator of signal transduction and cytoplasmic protease activity is reduced in the epidermis.

Subtypes

Types	Hyper proliferative Keratins (k6 &k 16)	profilaggrin	filaggrin
1	-	+	-
2	+	+	-
3	+	-	-

Clinical features:

Babies are usually born prematurely, sometimes as stillborn. Body is encased in a rigid , taut, hard, armour like, yellow brown adherent membrane. Shortly after birth broad, deep and intensively red fissures form in a geometric pattern. Head appears microcephalic, with

severe ectropion, conjunctival oedema, eclabion, rudimentary ear and nose, giving a grotesque appearance. Hands and feet are edematous and swollen,covered by mitten like casing, with well developed digits.

Pathology

Extraordinary thickened and compact orthokeratotic stratum corneum. Hair follicles show marked, concentric accumulation of keratotic material around hair shafts.

Electron microscopy show abnormal or missing lamellar bodies in the granular layer, absent extracellular lipid lamellae and presence of lipid inclusion or remnant organelles in the stratum corneum[39].

Prenatal diagnosis is possible by fetal skin biopsy, which demonstrates premature cornification at 20weeks of gestational age[40].

Outcome

Most patients do not survive more than few days, due to temperature instability and sepsis. In survivors, severe generalized ichthyosiform erythroderma eventuates[41]. Oldest child reported alive to date being 9 years[42].

LAMELLAR ICHTHYOSIS

Classical lamellar ichthyosis is inherited as an autosomal recessive disorder. But an autosomal dominant pattern of inheritance has been described[43].

Reported incidence is 1 per 1,00,000 live births.

Pathogenesis

It is due to deleterious mutation of the transglutaminase gene on chromosome 14q11, leading to transglutaminase-1 deficiency[44], which catalyzes the calcium dependent cross linking of proteins of cornified envelope, through γ glutamyl – lysine isopeptide bonds[45].

Pathology

Lamellar ichthyosis is a retention type ichthyosis.There is massive orthokeratotic hyperkeratosis with acanthosis and mild papillomatosis. Granular layer is normal or increased.

Electron microscopy shows elongated cholesterol clefts and translucent lipid droplets in stratum corneum with a thin or absent cornified cell envelope[46].

Clinical features

At birth the disease presents as collodion baby, followed by scaling within the first month of life. Erythroderma is usually less intense.

Scales are large, dark brown or grey, plate like, firmly adherent and form a mosaic or bark like pattern. Traction and compression by taut skin leads to scarring alopecia. Hair shafts are encased by thickened stratum corneum. Severe ectropion leads to exposure keratitis. Deep fissures in flexures cause limitation of joint movement, flexion contracture and sclerodactyly.

Other features are palmoplantar keratoderma, secondary nail dystrophy, severe heat intolerance due to epidermal constriction of sweat ducts and recurrent ear infection due to accumulation of scale in the external ear canal.

In mild lamellar ichthyosis, typical scales occur only in lower legs and upper arm. Fine white branny scales occur on the flexures and neck[47].

Autosomal dominant Lamellar ichthyosis

There is no collodion membrane at birth. These patients have non erythrodermic, lamellar type generalized scaling from birth, palmoplantar hyperkeratoses and lichenification of dorsa of hands and feet.

NON BULLOUS ICHTHYOSIFORM ERYTHRODERMA

Rare and usually severe autosomal recessive, inflammatory ichthyosis, although autosomal dominant transmission was reported. It is more common than lamellar ichthyosis, affecting 1 in 3,00,000 population.

Pathogenesis

Few patients carry recessive mutation in the transglutaminase1 gene, leading to abnormal formation of cornified cell envelope[48].

Ultrastructural and biochemical abnormalities such as an increased number of lamellar bodies, accumulation of lipid droplets,

abnormal activity of lamellar body enzymes in the stratum corneum, are suggestive of abnormalities in the lamellar body secretory system[49].

In some patients, inactivating mutations were identified in lipoxygenase-3 (ALOXE3) and 12- lipoxygenase (ALOX12B), which encode non heme, iron containing dioxygenases[50] which catalyzes the oxygenation of free and esterified polyunsaturated fatty acids, phospholipids and triglycerides, and are crucial for formation of epidermal lipid barrier.

Pathology

In the epidermis, there is variable mild parakeratosis and acanthosis with normal or prominent granular layer. Prominent blood vessels and mild upper dermal lymphocytic infiltrate are seen in the dermis.

Kinetic studies show increased epidermal turnover rate[51].

Using ultrastructural criteria Anton – Lamprecht described five phenotypes within the autosomal recessive ichthyosis group-"ichthyosis congenita".

Type I - Characterised by accumulation of numerous lipid droplets in the corneocytes. Clinical phenotype is that of erythroderma with fine scaling[54].

Type II – Characterized by accumulation of "cholesterol" crystals, and may corresponds to lamellar ichthyosis phenotype.

Type III – Characterized by reticulate scale pattern with erythroderma. Ultrastructurarly lamellated membrane structures are seen[55].

Type IV & V – Individual case reports.

Clinical features

Clinical spectrum is more variable with respect to severity. Collodion baby presentation is seen at birth in 90% cases and generalized scaly erythroderma is apparent after that. Scale is white or grey, thin, superficial and semi adherent and appear feathery in face, arm, trunk and lamellar on lower legs. Scaling may be cyclical with shedding over 2-4 weeks. Summer deterioration is often present.

Other features

Ectropion which may leads to exposure keratitis[52].

Palmoplantar hyperkeratosis(70%) with painful fissures.

Tinea amiantacea with patchy cicatrical alopecia[53].

Nail dystrophy, subungual hyperkeratosis (50%), onychomycosis

Hypohidrosis and heat intolerance.

Wide spread fungal infection reported.

Mild growth retardation.

Difference between non bullous ichthyosiform erythroderma and Lamellar Ichthyosis

Non bullous ichthyosiform erythroderma	**Lamellar ichthyosis**
Clinical	**Clinical**
Fine white scale	Thick plate like scale
Erythroderma (variable)	Erythroderma- little to absent
Epidermal turnover times	**Epidermal turnover times**
Accelerated mitotic rates	Normal proliferation kinetics
Increased epidermal labeling indices	
ultrastructural	**Ultrastructural**
Abnormal and increased number of lamellar bodies	Normal lamellar bodies
Numerous lipid droplets within cornified cells	Not seen
Extensive bilayer stacks within intercellular spaces of stratum corneum.	Not seen
Histopathology	**Histopathology**
Stratum corneum four times thicker	Stratum corneum massively thickened (nine times)
More parakeratosis	No parakeratosis
Prominent mucin or glycosaminoglycans in stratum corneum cell membranes	Normal granular layer
	No PAS+ membranes
Biochemical	**Biochemical**
Butyrase/glucosidase ratio 90 to 100	Butyrase/ glucosidase ratio < 5

BULLOUS ICHTHYOSIFORM ERYTHRODERMA OF BROCQ

Synonyms

Epidermolytic hyperkeratosis –The term was coined by Frost & Vanscott Bullous ichthyosis.

Rare autosomal dominant disorder with complete penetrance, which is associated with blistering in early phases. Sporadic occurrence is seen in 50% cases[56].

Estimated prevalence is 1 in 2,00,000.

Pathogenesis

K1 (Type II –basic) and k10 (Type I- acidic) are the keratins specific to the differentiated epidermis. BIE is caused by heterozygous mutation in the genes coding keratin 1 and 10, localized on chromosomes 12q11-q13 and 17q12-q21, respectively[57]. Pathogenic mutations, leading to nonconservative aminoacid substituitions, cluster at the boundaries of the α helical rod domains – 'hot spot arginine'[58]. Mutation perturb keratin alignment, oligomerization and filament assembly, thus weakening the cytoskeleton, compromising mechanical strength and cellular integrity of the epidermis. The association of desmosomes and tonofilaments is disturbed, so that many desmosomes are attached to only one keratinocyte instead of connecting two neighbouring keratinocyts. Real acantholysis occur leading to blister formation.

Keratin 1 mutations are usually associated with severe palmoplantar keratoderma, where as KRT10 mutations spare the palms and soles, because the gene is not expressed here.

Keratin filament disruption may impair lamellar body secretion resulting in an impaired barrier and secondary epidermal hyperplasia[59]. Epidermal hyperplasia results in expression of the alternate "hyperproliferative" keratin pair (k6 & k10) which could ameliorate the expression of k1 and k10 and the blistering phenotype, after the neonatal period .

Pathology

Nikolsky (1897) first recognized the characteristic histopathology of bullous ichthyosiform erythroderma known as epidermolytic hyperkeratosis or granular degeneration[61].

Epidermis shows marked hyperkeratosis and acanthosis. In the prominent and degenerate granular layer and in upper stratum spinosum, there are variously sized clear spaces around the nuclei. Peripheral to the clear spaces, cells show indistinct boundaries formed by irregular shaped keratohyaline granules. Intraepidermal bullae form through separation of edematous cells from one another[62].

Dermis shows moderately severe chronic inflammation. Labelling with tritiated thymidine show increased proliferative activity in the epidermis.

Clinical features

At birth, mild generalized erythroderma is present. Flaccid blisters and superficial erosions at sites of minor trauma are apparent within first few hours of life. Erosions heal rapidly without scarring.

During childhood, localized blistering at sites of trauma continues and erythroderma fades. Hyperkeratosis become obvious and is prominent around anterior neck, flexures, abdominal wall and scalp. Yellow brown waxy, ridged or corrugated scale sometimes forming spiny outgrowth builds up in the skin creases. Cobble stone like keratoses occur over dorsa of hands and feet.. Verrucous plaques are easily dislodged, leaving tender erosions. Skin colonization by staphylococcus, brevibacterium and fungi produces embarrassing body odour and repeated skin infection. Scarring alopecia may occur.

Palm and soles show hyperkeratosis in 60% and it may leads to recurrent painful, fissures and contracture. Clinical subtyping of bullous ichthyosiform erythroderma is based on the presence or absence of severe palmar / plantar hyperkeratosis.

Clinical subtypes of epidermolytic hyperkeratosis

Charact-eristic	NPS-1	NPS-2	NPS-3	PS-1	PS-2	PS-3
Palm/ sole Keratosis	–	–	–	+	+	+
Palm /sole surface	Normal	Normal	Hyper linear, Minimal scale	Smooth	Smooth	Cerebr-iform
Digital Contr-actures	–	–	–	–	–	–
Scale	Hystrix	Brown	Fine, white	Mild	White Scale, peel	Tan
Distri-bution	Genera-lized	Genera-lized	Genera-lized	Localize d	Genera-lized	Genera-lized
Erythro-derma	–	–	+	–	+	–
Blistering	+	+	+	Locali-zed	+	Neona-tal

Variants

Cyclic ichthyosis with epidermolytic hyperkeratosis

Annular epidermalytic ichthyosis[63]

Naevoid BIE – unilateral or bilateral streaks of hyperkeratosis that follow the lines of Blaschko[64] showing histological features of EHK. It is caused by somatic mutation in KRT1 or KRT10 ,arising postzygotically during early embryogenesis.

ICHTHYOSIS BULLOSA OF SIEMENS

Synonyms

Ichthyosis exfoliativa

Rare autosomal dominantly inherited ichthyosis.

Pathogenesis

It is due to heterozygous mutation in the gene for keratin 2e (KRT2e)[65], which is expressed only in the upper most spinous and granular layer of the epidermis.

Clinical features

At birth, the skin may appear normal or show mild blistering. Trauma induced small blisters on the extremities occur during infancy but usually subside during early childhood, while hyperkeratosis

develops. Predilection sites are the skin overlying the joints, flexures and the dorsa of the hands and feet, and there is always sparing of the palms and soles present. The skin may appear ridged, shiny or lichenified. A characteristic feature is superficially denuded areas with collarette-like borders described as ‘moulting’ or ‘mauserung’, which develop due to superficial blistering and shedding of the stratum corneum.

Histopathology

Features of epidermolytic hyperkeratosis are confined to the prominent granular layer and upper spinous layer. Sites of mauserung reveal intracorneal blistering with orthohyperkerotosis above and below the split.

ICHTHYOSIS HYSTRIX

It is a descriptive term for a clinically and genetically heterogenous group of skin disorders, characterized by spiny hyperkeratotic scale similar to that of BIE. They differ from BIE in that blistering is not a feature, erythroderma is usually mild or absent, and limited or naevoid forms are more common.

Clinical features

At birth there may be a generalized or naevoid scaly erythema. Hystrix (porcupine spine) scaling, often a muddy brown or grey color, accumulates during childhood and affects extensor aspects of the limbs

and truncal areas. Palmoplantar keratoderma either diffuse or striate, affects most people which may lead to functional impairment.

Variants

Icthyosis hytrix curth-macklin – due to mutation affecting V2 domain of keratin 1

Electron microscopy show characteristic continuous perinuclear tonofilament shell in the upper spinous and granular layer, resulting in three distinct cytoplasmic compartments. Double nuclei occur in 10% of spinous and granular keratinocytes.

IH of Rheydt – now known as HID syndrome, characterized by hystrix like ichthyosis and deafness.

COMEL NETHERTON'S SYNDROME

A rare autosomal recessive disorder that is characterized by the concurrence of ichthyosis, characteristic hair shaft abnormality and atopy[66]. 18% of all congenital erythrodermas were attributable to Netherton's syndrome[69].

Comel – described the clinical features of ichthyosis linearis Circumflexa[67].

Netherton – discovered the hair shaft abnormality[68].

Wilkinson – delineated the triad of clinical features.

Pathogenesis

It is due to mutation in the SPINK5 gene (serine protease inhibitor Kazal type 5) which encodes LEKT1 (lympho epithelial Kazal type related inhibitor) [70] which may be important in the down regulation of inflammatory pathways. Loss of LEKT1 leads to premature and uncontrolled proteolytic activity of serine proteases which could result in abnormalities of structure of lamellar lipid membrane[71].

In the hair, failure to convert sulphydryl groups to disulphide bonds leads to weak coherence of cortical cells. Such focal softening of hair shaft may allow invagination of distal shaft in to the dilated proximal cup.

Pathology

Varies with the type and phase of the lesion . .

Erythroderma –shows hyperkratosis, parakeratosis, exocytosis, spongiosis intraepidermal microabscesses and subcorneal split .

Double edged scale –show parakeratosis with reduced or absent granular layer. Focal accumulation of PAS positive, diastase- resistant, homogeneous material representing exuded serum is seen within the parakeratotic stratum corneum[72].

Older ILC lesions –show psoriasiform epidermal hyperplasia, Papillomatosis and a mixed perivascular

inflammatory infiltrate.

Microscopy of Hair – taken from scalp / eyebrow[73] show trichorrhexis Invaginata (bamboo hair) in 20 – 50% cases. It consists of a bulbous distal hair end invaginating a concave dilated proximal hair terminal giving a ball and socket appearance . Nodular thickening of the distal end of broken hair shafts ('golf tee')[74], pilitorti, trichorrhexis nodosa and helical hair may also be seen.

Clinical features

At birth generalized erythroderma is present and scaling quickly develops. In approximately 20% patients, complications like hypernatremic dehydration[75], temperature instability bronchopneumonia, sepsis, which may be fatal, occur. Failure to thrive and diarrhoea may occur resulting in short stature.

Erythema tends to improve but may recur. During child hood, 50% develop ichthyosis linearis circumflexa (ILC). It is an erythematous, scaly, annular or polycyclic, flat patch with an incomplete advancing double edge of peeling scale. It is episodic,often migrating in a cephalocaudal pattern. Fluctuating erythroderma triggered by intercurrent illness may occur and in between attacks, skin may look normal. Pruritus and flexural lichenification may occur. Impaired sweating can lead to hyperpyrexia. Bacterial, fungal infection and viral warts are common.

Atopy – Atopic diathesis is seen in 50% of patients and manifests as atopic dermatitis or asthma. Eosinophilia and allergic reactions to various foods are common. Serum IgE levels are markedly elevated ranging from 100 to 10,000 Iu/ml[76].

Hair – scalp, eyebrow, eyelash, body hair remain sparse, lustreless and brittle. Hair is unruly, short and spiky. Broken hair shafts at follicular orifice produces a peppered appearance.

Others – Intermittent amino aciduria[77], deficient IQ, seizures and impaired CMI.

Chronic erythroderma, with disabling flexural edema and papillomatosis may occur in the axilla, groin, vulva, which is premalignant.

SJÖGREN LARSSON SYNDROME

It is a rare autosomal recessive neurocutaneous disorder, comprising of congenital ichthyosis, spastic diplegia and mental retardation.

Pathogenesis

It is caused by deficiency of the microsomal enzyme fatty aldehyde dehydrogenase(FALDH), due to inactivating mutations in the FALDH gene, located on chromosome 17 p11.2[18]. This enzymes catalyzes the oxidation of long chain aliphatic aldehydes into fatty acids, a pathway that is important for the synthesis of epidermal lipids as well

as the catabolism of phospholipids and sphingolipids in the brain[79]. The symptoms of Sjogren-Larsson syndrome are thought to stem from membrane alterations due to accumulation of fatty alcohol or fatty aldehyde- modified lipids and proteins. Retarded myelination and a variable degree of dysmyelination probably results from the accumulation of free lipids in the periventricular white matter.

Pathology

Epidermis shows orthohyperkeratosis, acanthosis, and papillomatosis.

Granular layer may be normal or increased.

Electron microscopy may show lamellar membrane inclusions and cleft in corneocytes.

Clinical features

Skin – At birth skin is dry and mildly erythrodermic .Collodion baby presentation is rare[80]. Scaling develop within three months, tends to follow a cyclical pattern of accumulation and shedding, predominantly affecting limbs and face. Lamellar type ichthyosis occur in lowerlimbs. A velvety orange or brown lichenification topped with verrucous hyperkeratosis is seen in and around flexures, neck and periumbilical folds and is helpful in diagnosis. Perisistent pruritus may occur leading to visible excoriations. 70% patients develop palmoplantar keratoderma.

Neural

Symptoms are evident during first year of life. It is stable and nonprogressive. Features include spastic di or tetraplegia, mental retardation[81], speech defects, seizures and learning disability.

Ocular

Glistening dots on fovea and para fovea[82] of the retina, which do not interfere with vision, may develop during childhood and fade with advancing age. It is seen in 80% patients and occurs due to the deposition of lipofuscin pigment granules in the specialized retinal epithelium[83].

REFSUM'S DISEASE

Synonyms

Heredopathia atactica polyneuritiformis

Phytanic acid storage disease

A rare autosomal recessive neurocutaneous disorder.

Pathogenesis

This disorder is caused by inactivating mutations in both copies of the peroxisomal phytanoyl-CoA hydroxylase(PAHX) gene on the short arm of chromosomes 10[85]. Deficiency of the peroxisomal phytanoyl-CoA hydroxylase causes impaired degradation of phytanic acid, a 20-carbon, saturated, branched- chain fatty acid, exclusively derived from exogeneous sources like plant chlorophyll, leading to an excessive accumulation of phytanic acid in tissues and body fluids.

Normal serum level of phytanic acid is 1mg/ 100ml but in Refsum's disease, it accounts for 5 – 30% of serum lipids and level rises to 60mg / 100ml. Phytanic acid interferes with membrane structure and function[84].

Pathology

Besides nonspecific orthokeratotic hyperkeratosis, lipid containing vacuoles are seen in the basal keratinocytes .

Clinical features

Scales resemble ichthyosis vulgaris, which develop during childhood or adolescence. In late untreated cases, lamellar scaling develops. Hyperkeratosis of palms and soles may be seen.

Neural features

Start in childhood and progressive, but have undulating course with periods of acute exacerbation and remission. Features include failing night vision and concentric visual field constriction due to progressive retinitis pigmentosa, cataract, deafness, tinnitus,anosmia, progressive weakness, foot drop, cerebellar ataxia, mixed sensorimotor polyneuropathy with hypertrophied peripheral nerves and an elevated CSF protein.

Others

Renal tubular dysfunction, skeletal hyperostosis,cardiomyopathy leading to sudden death.

TAY'S SYNDROME.

Synonyms

IBIDS syndrome- ichthyosis, brittle hair, intellectual impairment, decreased fertility and short stature.

Trichothiodystrophy E,F.

Heterogeneous group of rare autosomal recessively inherited disorders, sharing sulfur deficient, short, brittle hair as a possible marker for neuro ectodermal disease.

Pathogenesis

There is reduced stability or altered function of the transcription/ repair complex TF11H, due to mutation in the genes, that encode helicase subunits ERCC2/ XPD and ERCC3/ XPB[86]. This leads to defective DNA repair leading to photosensitivity. The growth defects, brittle hair and nails, and neurological defects may be caused by impairment of transcription function of XPD and XPB gene products, leading to reduced RNA synthesis[87].

Reduced level (up to 50%) of hair sulphur and sulphur containing aminoacids, cysteine, methionine and proline are the hall mark of trichothiodystrophy. Based on cellular response to uvlight, three groups were identified.

1. Normal cell survival and excision repair after UV irradiation.

2. Repair synthesis was only 50 percent of normal and RNA synthesis was severely reduced but cell survival was normal.
3. A severe excision repair defect that appears to be identical to xeroderma pigmentosum complementation group D[203].

Pathology

Skin –In the epidermis there is hyperkeratosis, focal parakeratosis, acanthosis and a normal or reduced granular layer.

Hair

Light microscopy – hair shafts show transverse fractures (trichoschisis) . A nodal appearance similar to trichorrhexis nodosa or 180° twists as in pilitorti may be observed.

Polarizing light microscopy – gold standard for detecting the characteristic light and dark bands, the so-called 'tiger tail' or 'zigzag' pattern[88].

Transmission electron microscopy –may show an abnormal alignment of microfibers as well as an absence of the exocuticle and A-layer.

Clinical features

Skin

At birth, the disease presents with a collodion membrane or erythroderma in a premature neonate. Scales vary from fine, translucent to dark and large. Erythroderma improves after infancy. Other features are increased susceptibility to infection, follicular keratosis, erythema,eczema, pruritus, hypohidrosis, cheilitis, pyoderma,

folliculitis, palmar pustules, telangiectasia, poikiloderma. An elfin like and progeric face is seen due to fat atrophy with prominent ears and chin recession[89] . Photosensitivity occurs in 50% patients but there is no report of cutaneous malignancies[88].

Nails may show thinning, longitudinal ridging, yellow discolouration, onychogryphosis.

Hair

Hair may be broken, brittle, sparse, sometimes absent in scalp, eyebrow, eyelashes, axillary, pubis. Few nasal vibrissae and otic hairs are present. Marked susceptibility to weathering is present.

CNS

Mental retardation, seizures, tremor, ataxia, neurosensory deafness, dysarthria, spasticity, hemi-and tetraparesis, cerebellar deficiency, pyramidal signs, intention tremor, impaired motor coordination, peripheral neuropathy, nystagmus. Sociable behaviour is frequently seen[88].

Dental

Enamel hypoplsia and caries, maxillary hypoplasia, high-arched palate, bifid uvula, and leukoplakia.

Ophthalmologic

Antimongoloid slant, ectropion, conjunctivitis, hypertelorism, enophthalmus, exophthalmus, astigmatism, chorioretinal atrophy, retinal

pigmentation, pale optic disc, photophobia and diminished red-green discrimination.

Genital

Decreased fertility, cryptorchidism, hypoplasia of both male and female genitals, and hypospadiasis.

Orthopaedic

Genu valgum, coxa valga, valgus deformity of the great toe, cubital and tibial valgus deformity, pectus excavatum, scoliosis, thoracic kyphosis and lumbosacral lordosis.

Related syndromes

BIDS – Brittle hair, intellectual impairment, decreased fertility and short stature.

PIBIDS - Association with photosensitivity seen.

SIBIDS[90] – osteosclerosis, ichthyosis,brittle hair, intellectual impairment,decreased fertility and short stature.

X LINKED DOMINANT ICHTHYOSIS

Synonyms

Conradi-Hünermann- Happle syndrome

X linked dominant chondrodyplasia punctata type Π

Very rare, X linked dominant disorder,which be lethal to male fetuses but may be compatible with life in xxy karyotype. It is one of the variants of chondrodysplasia punctata.

Pathogenesis

It occurs due to primary defect in cholesterol biosynthesis. A deficiency of dihydroxyacetone phosphate acyl transferase enzyme which is responsible for synthesis of plasmalagen phospholipids and glycolipids is seen. Distinct mutation in the emopamil binding protein (EBP) on the short arm of the X chromosome, leads to accumulation of 8 dehydrochholesterol and 8(9)- cholesterol[91].

Pathology

In epidermis, orthohyperkeratosis with focal parakeratosis, reduced granular layer, prominent perifollicular atrophy in old cases are seen.

Electron microscopy may show needle like inclusions in the granular layer, persistant desmosomal structures in the stratum corneum, degenerate mitochondria and vacuolated lamellar bodies.

Clinical features

Typically females are affected. Babies are born with either collodion membrane or generalized ichthyosiform erythroderma which resolves within first year. Generalized linear and swirling patterns of erythroderma and scaling are established along Blaschko lines. In adults, hyperkeratosis is replaced by follicular atrophoderma and icepick scars, linear pigmentary changes and scarring alopecia all in a Blaschkoid distribution. Palmoplantar hyperkeratosis and nail dystrophy may occur[92]. Recurrent infection especially in the flexures is common.

Skeletal anamolies

Skeletal anomalies are usually asymmetric. They include frontal bossing, flat nasal bridge, facial asymmetry, shortening of limbs, scoliosis, hexadactyly. Widespread premature calcifications manifesting as stippled epiphyses involving the trachea and vertebrae may be seen on radiographs during infancy.

Others

Unilateral cataracts (60%), congenital heart defects, sensorineural deafness, central nervous system malformations and renal anomalies. Intellect is not impaired and life expectancy is normal. Spontaneous improvement with age may occur, which reflect progressive elimination of mutant cells by adjacent normal cells, which have a growth advantage.

Related syndromes

(1) Rhizomelic chondrodysplasia punctata – autosomal recessively inherited,characterized by combination of punctate epiphyseal calcification, rhizomelia (proximal limb shortening), deficient red blood cell plasmalogens, and accumulation of phytanic acid. Ichthyosis occur in 25% of patients which is similar to Conradi Hümermann syndrome.

(2) X linked chondrodysplasia punctata with steroid surfatase deficiency.

CHANARIN – DORFMAN SYNDROME

Synonym – Neutral lipid storage disease.

Autosomal recessively inherited, rare inborn error of lipid metabolism, characterized by ichthyosis, myopathy and vacuolated leukocytes[93].

Aetiology

Increased fibroblast triglyceride synthesis, with a complete failure of endogenous triglyceride breakdown has been demonstrated. Exogenous triglyceride metabolism and serum lipid levels are normal[94].

Pathology

Light microscopy –In peripheral smear there are numerous lipid containing vacuoles in the circulating granulocytes and monocytes but not in lymphocytes called 'Jordans anomaly'[96] is seen. Lipid staining of skin shows closely packed lipid droplets of varying sizes in epithelium of eccrine sweat glands and ducts, basal cells, fibroblast and endothellial cells. Biopsy of muscle, liver, and bone marrow also reveal lipid droplets.

Ultastructure – Epidermal lamellar bodies and intercellular lipid lamellae are disturbed by globular electron lucent inclusions[96].

Clinical features

Babies are either collodion or erythrodermic at birth,and scaling resemble that of non bullous ichthyosiform erythroderma. Troublesome pruritus hypohidrosis,and flexural lichenification may occur.

Others

Subclinical to marked proximal myopathy with elevated muscle enzymes, hepatomegaly with abnormal liver enzymes, cataract of nuclear type (50%), nerve deafness, ataxia, short stature, mental retardation.

KERATITIS ICHTHYOSIS DEAFNESS SYNDROME

Synonym

Erythro keratodermia progressive of Burns.

Skinner (1981) – coined the acronym 'KID'[97]

Majority of the cases are sporadic and there is overlap with ectodermal dysplasias seen..

Pathogenesis

Caused by missense mutations in the connexin gene GJB2 encoding the gap junction protein 26[98].

Pathology

Orthohyperkeratosis, acanthosis, papillomatosis and vacuolization of the cells in the granular layer are seen.Corneal epithelium may be dyskeratotic, atrophic or absent in the center, and Bowman,s membrane may be absent. In the inner ear, the organ of corti is immature or atrophic.

Ultrastructural study may show changes similar to ichthyosis hystrix.

Clinical features

Transient erythroderma is present at birth. During infancy, fixed, symmetrically distributed, well demarcated, hyperkeratotic plaques with an erythematous base and a leathery rough verrucous surface develops in face usually cheeks, forehead, ear, chin, nose, small joints.Thick perioral rugae and leonine facies may occur. Prominent follicular hyperkeratosis with scarring alopecia of scalp[99], loss of eyebrows, eye lashes and body hair occur. A reticulated PPK resembling grained leather is characteristic. Nails may be dystrophic and show leukonychia. Absent teeth, delayed eruption and cavities may occur. Acneform eruptions, deep abscesses and discharging sinuses, chronic cutaneous granulomatous candidial and fungal infection may develop. Squamous cell carcinomas may develop even in childhood[100].

Others

Sensorineural deafness during infancy, progressive corneal vascularization (96%) leading to blindness by adolescence may be seen.

Variants

HID syndrome – Allelic variant of KID, characterized by hystrix like ichthyosis and deafness.

CHILD SYNDROME

The acronym CHILD describes a very rare disorder comprising congenital hemidysplasa, ichthyosiform erythroderma, and limb defects, which is found almost exclusively in females[104].

Pathogenesis

It is an X linked dominant disorder. Inactivating mutations in NSDHL(NADH steroid dehydrogenase like protein) which encodes the enzyme 3ß – hydroxysteroid dehydrogenase has been demonstrated[105]

Pathology

Marked ortho and parakeratosis with acanthotic and papillomatous epidermis with neutrophilic collection in stratum corneum overlying a mild superficial perivascular infiltrate is seen. Multiple layers of granular cells surround the sweat ducts, while the granular zone in the surrounding epidermis may be absent, normal or thickened.

Clinical features

Child presents at birth or neonatal period with a unilateral erythema with hyperkeratosis, crusted plaques covering most of one side of body, commonly on right side, with a sharp demarcation in midline, sparing the face with affinity for the skin folds (ptychotropism). Linear bands of ichthyotic skin may occur in the other side due to somatic mutation[106]. Linear alopecia of the affected side and claw like nail dystrophy are common. The lesions often improves with time.

Skeletal system

Anamolies include hypoplasia of digits, ribs, ipsilateral limb hypoplasia, spina bifida scoliosis. Stippled epiphyses analogous to Conradi Hünermann syndrome has been noted.

Others - Renal defects[107], CNS, and CVS malformations.

Ichthyosis follicularis with alopecia and photophobia

It is characterized by non inflammatory follicular keratoses, persistent non cicatrical scalp and body alopecia and severe photophobia from birth.Generalised xerosis and lamellar scaling are common. Lesions must be distinguished from keratosis follicularis spinulosa decalvans and keratosis pilaris rubra atrophicans facei.

CHIME syndrome

Coloboma, heart disease, ichthyosis, mental retardation and ear defects.

Kallmann's syndrome – caused by large deletion of the short arm of the X chromosome proximal to and involving the STS gene.Characterized by XLRI with hypogonadotrophic hypogonadism, anosmia, nystagmus, synkinesis[101]. Other features are developmental delay, spastic paraplegia, osteoporosis.

Rud's syndrome – X linked ichthyosis, obesity, hypogonadism, mental retardation, epilepsy and endocrinopathies[102].

ICE syndrome – AD, characterized by ichthyosis vulgaris like eruption, 'full' cheeks, sparse lateral eyebrows, craniofacial and skeletal abnormalities[103].

Multiple sulfatase deficiency

Rare autosomal recessive disorder characterized by a deficiency of several sulfatides, glycosaminoglycans, spingolipids, steroid sulfates

in tissues and body fluids[108]. Clinical features include neurologic deterioration, skeletal abnormalities, facial dysmorphism and ichthyosis resembling that of X linked steroid sulfatase deficiency.

TREATMENT

Regular, paraffin based emollient application is of benefit to all ichthyosis patients. Urea containing emollients improve epidermal hydration and lyse keratin. Emollients are of limited value in bullous ichthysiform erythroderma as the scale is often waxy and macerated.

Keratolytic agents such as 1-5% salicylic acid can be used to encourage shedding of scale. Alpha-hydroxy acids, such as lactate, glycolic, malic, mandelic, citric, pyruvic, gluconic and tartaric acid enhance corneocyte shedding by virtue of their effect in breaking intercellular bonds[108].

Topical calcipotriol has been efficacious with lamellar ichthyosis[109].

Topical tacrolimus 0.1% produce significant improvement in Netherton's syndrome

Systemic retinoids are effective in most patients with severe congenital ichthyosis except in Netherton's syndrome, where

deterioration with systemic retinoid theropy is noted. The starting dose of acitretin is 0.5-0.75mg/kg/day and the maintenance dose is titrated down to the lowest effective level between 0.1 and 0.5mg/kg/day.

AIMS OF THE STUDY

- ✓ To study the incidence of Congenital ichthyosis in pediatric age group in Institute of child health, Government General Hospital, Chennai during the period of two years between september 05 to september 07.

- ✓ To study the incidence of various types of congenital ichthyosis and ichthyosiform syndromes.

- ✓ To study the age of onset of various types of congenital ichthyosis.

- ✓ To study the sex incidence of various types of congenital ichthyosis.

- ✓ To study the presenting symptoms and clinical patterns.

- ✓ To study the associated skin disorders with particular reference to atopy, keratosis pilaris, and fungal infection.

- ✓ To study the histopathological pattern.

- ✓ To study the prevalence of ichthyosis in family members.

MATERIALS AND METHODS

Materials for this study were gathered from the pediatric out patient wing of dermatology, Institute of child health, Government general hospital, Chennai during the period between September 05 to September 07. A total of 64 cases of ichthyosis were enrolled in the study on the basis of clinical pattern. The total number of new patients who attended the department during the period was enrolled for comparative studies.

Procedure

History

In eliciting the history, a set pattern of questionnaire was followed (as given in proforma). Enquiries were made with regard to symptoms, age of onset, duration, history of collodion baby, blisters, seasonal variation, repeated skin infection and atopy. History regarding involvement of other systems like central nervous system, skeletal system was taken.

Clinical examination

A careful and detailed dermatological and systemic examination with necessary investigations was conducted methodically. Patients up to fourteen years of age, were examined for distribution and nature of scales, presence of erythroderma, and blisters along with a note of associated disorders if any. Referral to other specialties like neurology and opthalmology were done to confirm or to rule out associated features of some syndromes as and when suspected.

Exclusion criteria

Acquired ichthyosis – Malnutrition

Congenital hypothyroidism

Acquired immune deficiency syndrome

Laboratory investigations

Routine hematological investigation was done in all cases. Microscopic examination of hair was done. Skin biopsy was done and specimens were studied with H & E stain.

All the datas were compiled and the inference was drawn .

OBSERVATION AND RESULTS

Incidence

Out of 10,200 patients attended dermatology out patient department, Institute of child health, Government General Hospital during the period between September 2005 and September 2007, total number of patients with congenital ichthyosis was 64.

Incidence of congenital ichthyosis was 0.63% or 6 per 1000.

TABLE – 1

Total number of patients attended as skin out patients at Institute of child health, Government General Hospital (sep 05 to sep 07)	10,200
Total number of patients with congenital ichthyosis	64
Incidence of congenital ichthyosis	0.63%

Different types of congenital ichthyosis and their incidence

Incidence of different types is as follows:

Ichthyosis vulgaris : 1 per 200

Lamellar ichthyosis : 9 per 10000

Non bullous ichthyosiform erythroderma : 4 per 10000

Bullous ichthyosiform erythroderma : 2 per 10000

Netherton's syndrome : 1 per 10000

Sjogren Larsson syndrome : 2 per 10000

TABLE – 2

S.No	Clinical types	No of Cases	Percentage
1	Ichthyosis vulgaris	46	0.45%
2	Lamellar ichthyosis	9	0.09%
3	Nonbullous ichthyosiform erythroderma	4	0.04%
4	Bullous ichthyosiform erythroderma	2	0.02%
5	Netherton's syndrome	1	0.01%
6	Sjogren Larsson syndrome	2	0.02%

Relative incidence of different types of congenital ichthyosis

Out of 64 patients with congenital ichthyosis, ichthyosis vulgaris accounts for 72% followed by lamellar ichthyosis 14%. Non bullous ichthyosiform erythroderma constitutes 6% followed by bullous ichthyosiform erythroderma and Sjogren Larsson syndrome each constitutes 3%. Netherton's syndrome constitutes 1.5% of cases.

Table – 3

S.No	Clinical types	No of Cases	Percentage
1	Ichthyosis vulgaris	46	71.8%
2	Lamellar ichthyosis	9	14.1%
3	Non bullous ichthyosiform erythroderma	4	6.3%
4	Bullous ichthyosiform erythroderma	2	3.1%
5	Netherton's syndrome	1	1.5%
6	Sjogren Larsson syndrome	2	3.1%

Sex incidence of different types of ichthyosis

Incidence of ichthyosis vulgaris was almost equal in both sexes. Incidence of lamellar ichthyosis was more in females. Equal sex distribution was seen in non bullous ichthyosiform erythroderma. Bullous ichtyosiform erythroderma, Sjogren Larsson syndrome and Netherton's syndrome were seen only in males.

TABLE – 4

S.No	Clinical Type	M	F	Total
1	Ichthyosis vulgaris	25	21	46
2	Lamellar ichthyosis	2	7	9
3	NBIE	2	2	4
4	BIE	2	_	2
5	Sjogren Larsson Syndrome	2	_	2
6	Netherton's syndrome	1	_	1
	Total	34	30	64

Age of onset of different types of ichthyosis

All except two cases of ichthyosis vulgaris had age of onset from three to six months. Lamellar ichthyosis, non bullous ichthyosiform erythroderma, bullous ichthyosiform erythroderma, and other ichthyosiform syndromes had age of onsets since birth.

TABLE – 5

Types of Ichthyosis	Months			
	Birth	3 months	6 months	1 year
Ichthyosis vulgaris	-	22	22	2
Lamellar ichtyosis	9	-	-	-
NBIE	4	-	-	-
BIE	1	-	-	-
Sjogren Larsson syndrome	2	-	-	-
Nethertron's syndrome	1	-	-	-

Evolution of collodion baby

Out of 13 collodion babies, 70% evolved in to lamellar ichthyosis and 30% patients evolved in to non bullous ichthyosiform erythroderma.

Types of ichthyosis	Number of cases	Percentage (%)
Total number of collodion babies	13	
Lamellar ichthyosis	9	70
Non bullous ichthyosiform erythroderma	4	30

TABLE – 6

Prevalence of consanguinity in different types of ichthyosis

In ichthyosis vulgaris 76% of patients had no history of consanguinous marriage of the parents and in 24% patients, history of second and third degree consanguinous marriage was present. In lamellar ichthyosis, non bullous ichthyosiform erythroderma, Sjogren Larsson syndrome, and Netherton's syndrome all the patients had consanguinous parents. In bullous ichthyosiform erythroderma history of 3^0 consanguinity of the parents was present in 50% of the patients.

TABLE – 7

Degree of consanguinity	Types of Ichthyosis											
	Ichthyosis vulgaris		Lamellar Ichthyosis		Non bullous ichthyosifom Erythroderma		Bullous Ichthyosifom erythroderma		Sjogren Larsson syndrome		Netherton's Syndrome	
	N	%	N	%	N	%	N	%	N	%	N	%
No	35	76	-		-		1	50	-		-	

2^0	2	4	4	45	2	50	-		1	50	1	100
3^0	9	20	5	55	2	50	1	50	1	50	-	

Associated conditions

Associated disorders seen with congenital ichthyosis were as follows;

TABLE – 8

Associated disorders	No of Patients
Atopy	4
Keratosis pilaris	3
Impetigo	5
Intertrigo	1
Café au lait macule	4
Rickets	1

Prevalance of ichthyosis in family members

In ichthyosis vulgaris, 41% of the patients had family history of ichthyosis. In lamellar ichthyosis, positive family history was present in 22% of the patients.

TABLE – 9

Types of Ichthyosis	Similar lesions in family members							
	Father		Mother		Sibling		Grandparents	
	N	%	N	%	N	%	N	%
Ichthyosis vulgaris	5	11	3	6.5	9	19.5	2	4.3
Lamellar ichthyosis	-	-	-	-	2	22	-	-
Non bullous ichthyosiform erythroderma	-	-	-	-	-	-	-	-
Bullous ichthyosiform erythroderma	-	-	-	-	-	-	-	-
Sjogren	-	-	-	-	-	-	-	-

Larsson synd rome								
Nether ton's synd rome	-	-	-	-	-	-	-	-

Lab Investigations

Percentage of patients with eosinophilia in ichthyosis vulgaris was 11%

Table 10

S.No	Type of ichthyosis	No of patients with eosinophilia	Percentage
1	Ichthyosis vulgaris	5	11
2	Netherton's syndrome	1	100

Serum IgE level

Serum IgE level was elevated (2000 IU/ml) in Netherton's syndrome patient.

DISCUSSION

In this study of 64 patients, the incidence of congenital ichthyosis was found to be 6 per 1000 (Table 1).

Incidence of various clinical types of congenital ichthyosis were as follows. (Table 2)

Ichthyosis vulgaris	: 1 per 200
Lamellar ichthyosis	: 9 per 10000
Non bullous ichthyosiform erythroderma	: 4 per 10000
Bullous ichthyosiform erythroderma	: 2 per 10000
Netherton's syndrome	: 1 per 10000
Sjögren Larsson syndrome.	: 2 per 10000

A study by Wells and Kerr CB showed, that the incidence of ichthyosis vulgaris may be as common as 1 in 250. In this study, the incidence of ichthyosis vulgaris was 1in 200 which complies with the above study.

Out of 64 cases, the relative incidence of different types of congenital ichthyosis were as follows. (Table 3)

Ichthyosis vulgaris	: 71.8%
Lamellar ichthyosis	: 14%
Non bullous ichthyosiform erythroderma	: 6%
Bullous ichthyosiform erythroderma	: 3%
Netherton's syndrome	: 1.5%
Sjögren Larsson syndrome	: 3%

Sex incidence of ichthyosis vulgaris and non bullous ichthyosiform erythroderma were equal in this study (Table 4). But females had increased incidence than males (1:3) in lamellar ichthyosis,In Netherton's syndrome and Sjögren Larsson syndrome only males were affected in this study.

Age of onset of ichthyosis vulgaris was around 3-6 months in 96% patients (Table 5). In lamellar ichthyosis , non bullous ichthyosiform erythroderma, bullous ichthyosiform erythroderma , the age of onset of the disease was from birth. This complies with that of the description about the age of onset of diseases given by Traupe et al, in the guide to clinical diagnosis of ichthyosis.

In Vangysel study of follow up of 17 cases of collodion baby, 60-80% of the infants developed non bullous ichthyosiform erythroderma and lamellar ichthyosis. In this study of 13 cases of

collodion babies, 70% of the patients developed lamellar ichthyosis and 30% of the patients developed non bullous ichthyosiform erythroderma . Thus the ratio of non bullous ichthyosiform erythroderma Vs bullous ichtyosiform erythroderma was 1:2**.** 3

(Table 6).

The most common presenting complaints of the patients were dryness, roughness and disfigurement. Apart from that, itching was present in patients with associated atopy. Winter exacerbation of the disease was present in 46% of ichthyosis vulgaris patients.

A study by Kuokanen et al showed an association of atopy in 37-50% of patients. In this study 6.5% patients had associated atopy and other associations seen were kerotosis pilaris, café au lait macules, pyoderma, intertrigo and dermatophytosis. (Table 8)

There were several reports of individual cases with congenital ichthyosis occurring in association with extra cutaneous defects. In this study, a patient with ichthyosis vulgaris had associated rickets.

In ichthyosis vulgaris, 76% of patients had no history of consanguinous marriage of the parents and in 24% of patients, history of 2^0 and 3^0 consanguinous marriage was present. (Table 7). In lamellar

ichthyosis, 2^0 consanguinous marriage was present in 44% of patients and 3^0 consanguinous marriage was present in 55% of patients. In non bullous ichthyosiform erythroderma, 50% patients had 2^0 consangiunous parents and 50% had 3^0 consanguinous parents. This complies with that of autosomal recessive inheritance.

In bullous ichthyosiform erythroderma, 50% had no history of consanguinity and 3^0 consanguinity was present in 50% patients. In Netherton's syndrome, 2^0 consanguinous marriage was present in the parents and it complies with that of autosomal recessive inheritance. In Sjögren Larsson syndrome, 2^0 consanguinous marriage was present in 50% of patients and 3^0 consanguinous marriage was present in 50% patients and it complies with that of autosomal recessive inheritance.

In ichthyosis vulgaris, family history of ichthyosis was present in41% of patients (Table 9). In lamellar ichthyosis, positive family history was present in one family where two siblings were affected. As it is a autosomal dominantly inherited disorder, the risks of having a further affected child is 25% which is seen in this case.

In bullous ichthyosiform erythroderma, no family history of ichthyosis was present in the patient. Because it is a autosomal

dominantly inherited disorder it can be presumed that the patient suffered a new keratin gene mutation.

Histopathological examination of biopsy from the patients with ichthyosis vulgaris showed features of hyperkeratosis with decreased granular layer. In bullous ichthyosiform erythroderma intra epidermal cleavage with vacuolated cells in the granular layer were seen. Hair shaft examination in Netherton's syndrome showed trichorrhexis invaginata of hair shaft in scalp hair sample.

Laboratory examination showed increased eosinophil count in 11% of ichthyosis vulgaris patients (Table 10). Serum IgE level was elevated (2000 IU/ ml) in patient with Netherton's syndrome.

Conclusion

- The incidence of congenital ichthyosis in Institute of child health, Government General Hospital during the period between September 2005 and September 2007 was 6 per 1000.

- The incidence of various clinical types of congenital ichthyosis were as follows

  Ichthyosis vulgaris : 1 per 200

  Lamellar ichthyosis : 9 per 10000

  Non bullous ichthyosiform erythroderma : 4 per 10000

  Bullous ichthyosiform erythroderma : 2 per 10000

  Netherton's syndrome : 1 per 10000

  Sjögren Larsson syndrome. : 2 per 10000

- The relative incidence of various clinical types of congenital ichthyosis were as follows

  Ichthyosis vulgaris : 71.8%

  Lamellar ichthyosis : 14%

Non bullous ichthyosiform erythroderma : 6%

Bullous ichthyosiform erythroderma : 3%

Netherton's syndrome : 1.5%

Sjögren Larsson syndrome : 3%

- Sex distribution was equal in ichthyosis vulgaris patients. In lamellar ichthyosis, the male to female sex ratio was 1:3

- The age of onset of ichthyosis vulgaris was around 3 to 6 months in 96% of patients. In other clinical types, the age of onset was from birth.

- Follow up of collodion baby showed that 70% of patients developed lamellar ichthyosis and 30% of patient developed non bullous ichthyosiform erythroderma, the ratio being 1:2.3.

- The main complaints of the patients were dryness, roughness and disfigurement. Winter exacerbation of the disease was present in 46% of ichthyosis vulgaris patients.

- 6.5% of the patients with ichthyosis vulgaris had associated atopy.

- Other associated condition seen were keratosis pilaris, café au lait macules, pyoderma and intertrigo.

- Rickets was seen in association with ichthyosis vulgaris in one patient.

- Ichthyosis was prevalent in family members of 41% of the patients with ichthyosis vulgaris and in 22% of the patients with lamellar ichthyosis.

- Laboratory investigations showed eosinophilia in 11% of patients with ichthyosis vulgaris. Serum IgE was elevated in patient with Netherton's syndrome.

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PROFORMA

DATE : **INFORMANT:**

CASE NO : **ADDRESS :**

NAME :

AGE :

SEX :

COMPLAINTS:

HISTORY OF PRESENT ILLNESS

Scaling – age of onset/ distribution

Course of lesion- tends to improve/ persistent/ remission

Seasonal variation- summer / winter exacerbation/

cyclical shedding or peeling

H/o blisters

H/o itching

H/o diminished sweating and heat intolerance

H/o photosensitivity/ photophobia

H/o repeated skin infections

H/o seizures

History s/o mental retardation

H/o difficulty in speech.

H/o difficulty in hearing

H/o disturbance in vision

H/o disturbance in perception of smell

H/o difficulty in walking

H/o any abnormal movements

H/o restriction of limb movements

H/o difficulty in climbing upstairs

H/o diarrhea/ malabsorption

History s/o atopy/ asthma

BIRTH HISTORY

ANTENATAL – Maternal illness / medication/ investigation

NATAL – Prematurity / Prolonged labour

NEONATAL – collodion baby / erythrodermic / blisters

DEVELOPMENTAL HISTORY

MILE STONES – social smile/ head control/ sitting with and without

Support / standing with and without support/

Walking / speech

FAMILY HISTORY

Pedigree chart

Consanguinous marriage of parents

Similar lesions in parents/ siblings

GENERAL EXAMINATION

Nourishment

Anemia

Jaundice

Lymphadenopathy

Short stature Height for age

Microcephaly Weight for age

Cataract Head circumference

Gait

Bony deformity

SYSTEM EXAMINATION

Central nervous system – higher function/ speech/ hearing / Nystagmus / hypertonicity / thickened peripheral nerves

Respiratory system

Cardio vascular system

Abdomen - hepatosplenomegaly

DERMATOLOGICAL EXAMINATION

SCALES

Small / large

White / dark

Loose / adherent

Lamellar / warty

Site – scalp / face / neck / trunk / upper & lower limb / cubital & popliteal fossa.

Blister / erosion

Erythroderma

Lichenification

Ectropion / Eclabion

Ear deformity / crumpled ears

Eczema / kerotosis pilaris / fungal infection / impetigo / wart

HAIR – alopecia / tinea amiantacea / brittle hair

NAIL – nail dystrophy

PALM / SOLE – hyperlinearity/ Palmoplantar keratoderma /
digital contracture/ sclero dactyly

GENITALS – Testicular descend

INVESTIGATIONS

Urine – albumin, sugar.

Blood – TC,DC, Hb%,ESR,Peripheral smear
LFT

X RAY

Skin biopsy

Microscopic examination of hair

Opthal opinion

ENT opinion

Neurology opinion

Endocrinology opinion

Clinical photographs

KEY TO MASTER CHART

F	- Female
M	- Male
ICH VULG	- Ichthyosis vulgaris
LI	- Lamellar ichthyosis
BIE	- Bullous ichthyosiform erythroderma
NBIE	- Non bullous ichthyosiform erythroderma
SJO LAR	- Sjogren Larsson syndrome
Nether synd	- Netherton's syndrome
Mon	- Month
Y	- Year
B	- Birth
SIB	- Sibling
MO	- Mother
Gra Fa	- Grand Father
Med	- medium
SE	- Summer exacerbation
WE	- Winter exacerbation
HL	- Hyper linearity
PPK	- Palmoplantar keratoderma
AD	- Atopic dermatitis
KP	- Keratosis pilaris
CALM	- café au lait macule
TI	- Trichorrhexis invaginata
Eos	- eosinophils